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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/995,263	Applicant(s) ONYUKSEL ET AL.	
	Examiner Gollamudi S Kishore, PhD	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *01 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The request for the extension of time and amendment filed on 10-10-03 are acknowledged.

Claims included in the prosecution are 1-31.

Double Patenting

I. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 15-25 and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 and 4-6 of U.S. Patent No. 6,197,333. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons: claims in said patent are product by process claims and the process is the same as instant process; the sizes of less than 300 nm in the claims of said patent fall within 'less than 100 nm' in instant claims. Instant VIP in claim 24 falls within 'therapeutic agent' claimed in claim 4 of said patent.

3. Claims 15-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,348,214. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons: instant claims and claims in said patent are drawn to a process of preparation of liposomes using the same lipid components. The limitation 'echogenic' recited in instant claims therefore is deemed to be included in the generic liposomes recited in the claims of said patent.

Applicant's arguments that obviousness type double patenting may only be made with a comparison of the claims in the cited patents and in this application and not the specification are not persuasive since the rejections are made on the basis of claims themselves and not based on the specification. The rejections are maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 5-25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paul (5,770,570) in view of Martin (5,225,212).

Paul discloses liposomal compositions containing VIP. According to Paul, these compositions are to be used for the treatment of diseases such as ischemia and mental conditions. VIP is either encapsulated within the liposome or bound on the liposome (note the abstract, col. 3, line 65 through col. 5, line 20, Examples and claims).

What is lacking in Paul is the binding of the phospholipid to PEG.

Martin discloses a method of preparation of liposomes by mixing the phospholipids, which include a phospholipid, which is bound to a water-soluble polymer (note the abstract, col. 3, line 1 through col. 4, line 10; col. 10, line through col. 11, line 62 and claims). Martin does not specifically teach that the drug can be loaded after the formation of liposomes. Martin however, on columns 10 and 11 appear to imply that the drug can be loaded by different methods. According to Martin, PEG extends the circulation time of the liposomes (note the abstract).

The inclusion of PEG taught by Martin in the liposomes of Paul for the preparation of liposomes containing VIP and use these liposomes for the treatment of disease states such as ischemia would have obvious to one of ordinary skill in the art since PEG extends the circulation time of the liposomes as taught by Martin.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that although the disclosure of Paul describes liposomal compositions containing VIP to be used in the treatment of diseases, it is silent with

respect to VIP with a sterically stabilized liposome. Thus, according to applicant, there would be no expectation of success that a sterically stabilized liposomes with VIP would be biologically active because PEG may interfere with VIP/receptor binding due to the size of PEG in relation to the size of VIP. This argument is not found to be persuasive because Martin's disclosure deals with liposomes containing PEG and Martin on col. 11, lines 35-62 teaches the usefulness of the invention in delivering biologically sensitive proteins. Martin also teaches through examples the effectiveness of PEG-liposomes using proteins such as vasopressin and colony stimulating factor (CSF). In this context, the examiner cites the reference of Tagawa (5,264,221) which discloses the retention of the functional ability of the monoclonal antibodies attached to the surface of liposomes also bonded with PEG (examples 2 and 3). Therefore, one of ordinary skill in the art would expect success with other proteins such as VIP. Furthermore, applicant's claimed proteins include "VIP/growth hormone releasing factor or IL-2 family of peptides including peptide fragments and analogs" and if applicant's rationale were to be applicable, one can question the expectation of success with so many proteins falling within the family of proteins claimed by applicant.

With regard to applicant's arguments that neither Paul nor Martin disclose or suggest that loading a compound to a preformed sterically stabilized liposomes is desirable or even attainable, the examiner points out that instant claims are drawn to a method of treatment using a product wherein VIP is on the surface of liposome. Although the claims recite product by process, they are still a method of treatment claims using a product wherein VIP is on the surface of liposomes and according to Paul, VIP is on the surface of liposomes. In essence, applicant has not demonstrated unexpected results in the treatment of various claimed disease states using VIP bound liposomes formed by applicant's specific process as opposed to prior art processes.

6. Claims 1-3, 5-25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paul (5,770,570) in view of Martin (5,225,212), further in view of either of Caras (5,374,548), Noda (BBA, 1994) and Keder (J. Immunotherapy, 1994) by themselves or taken together.

The reference of Caras shows that the drug can be loaded on to the already formed liposomes (note example 4).

Similarly, Noda teaches incubation of already formed liposomes with VIP to load VIP (note the abstract and page 325, col.1).

Keder discloses a process of preparation of liposomes and loading cytokines. The method involves the formation of liposomes and incubating the liposomes with IL-2 (note the abstract and page 49 and col. 1).

It would have been obvious to one of ordinary skill in the art to add a drug to the preformed liposomes of Martin with the expectation of obtaining similar results, since Martin himself teaches that the liposomes can be made by any art known method and the references of Caras, Noda and Keder show that the liposome formulations and technique of such loading are art known.

The examiner has already addressed applicant's arguments with regard to Paul and Martin. Applicant's arguments that the disclosures of Caras, Noda, and Keder describe loading of compounds to a preformed liposomes, but does not teach or suggest the use of sterically stabilized liposomes are similar to those raised for Paul and therefore, the same response is applicable.

7. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paul in view of Martin (5, 225212) or Paul in view of Martin (5,225,212) in further view of Caras, Noda and Keder cited above, further in view of Kirby (Biotechnology, 1984 of record).

Martin's method does not involve dehydration and rehydration of the liposomes.

Kirby while disclosing a method of preparation of liposomes by dehydrating the lipid vesicles and then rehydrating them, teaches that such a method would result in a uniform sized liposomes and that the method is simple and can be used on an industrial scale (note pages 979 and 983).

The introduction of the dehydration-rehydration procedure in the method of preparation of liposomes of Martin would have been obvious to one of ordinary skill in the art because of the advantages of such a step taught by Kirby.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments with regard to Paul and Martin. Applicant argues that Kirby does not correct the defect in Paul, Martin, Noda, Caras or Keder. This argument is not found to be persuasive since this reference is combined for its teachings of the advantages of using the dehydration and rehydration of the liposomes and the advantages would be the same irrespective of the active agents used and applicant has not shown otherwise.

8. Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paul in view of Martin (5, 225212) or Paul in view of Martin (5,225,212) in further view of Caras, Noda and Keder cited above, further in view of Lanza (5,612,057).

The primary references do not teach a diagnostic method using the liposomes. The use of liposomes as the diagnostic agents would have been obvious to one of

ordinary skill in the art, with the expectation of obtaining similar results, since the reference of Lanza shows the routine use of liposomes for diagnostic purposes.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments with regard to Paul and Martin. Applicant argues that Lanza does not correct the defect in Paul, Martin, Noda, Caras or Keder. This argument is not found to be persuasive since this reference is combined for its teachings of the use of liposomes for diagnostic purposes and therefore, one of ordinary skill in the art would expect reasonable success using the liposomes for diagnostic purpose.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is 703 308 2440. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703 308 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.

/S Kishore/

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK